## REMARKS

Claim 6 has been amended to recite that the complements claimed are "full length" complements. Although Applicants had requested the addition of priority information on the utility application transmittal filed with this application, Applicants have amended the specification to contain the priority application information in a more appropriate format. The specification also was amended as required by the Examiner to add the patent number for the second patent application referred to on page 4. No new matter has been added.

### Rejections Under 35 U.S.C. 112, First Paragraph

Enablement

The Examiner rejected claims 6, 37-40, 58, 63 and 67 under 35 U.S.C. 112, first paragraph, as not enabled by the specification. Applicants respectfully traverse the rejection.

Whereas Applicants elected SEQ ID NO:2 for examination, the Examiner bases the rejection on an alleged lack of teaching in the specification or objective evidence that SEQ ID NOs:3 and 4 are translated to SEQ ID NOs:1 and 2 (see first full paragraph on page 4 of the Office Action). First, SEQ ID NOs:1 and 2 are nucleotide sequences, not amino acid sequences. Second, Applicants do not understand the relevance of SEQ ID NO:3 or 4 to the enablement of a protein encoded by SEQ ID NO:2. Accordingly, Applicants respectfully assert that the alleged basis for lack of enablement is not valid.

Applicants have assumed for the purposes of responding to this Office Action that the Examiner meant to indicate that specification does not teach that SEQ ID NO:2 is translated into protein. If that assumption is correct, Applicants respectfully disagree. First, the nucleic acids described in the application, including SEQ ID NO:2, were isolated using the SEREX methodology. SEREX uses antibodies found in patient sera to clone sequences that encode proteins recognized by the antibodies. Therefore, the proteins must have been actually translated into proteins because the antibodies were produced in patients in response to the expression of the proteins. Without expression of the proteins, the cancer patients' sera would not contain specific antibodies that recognize the proteins. Second, the rejection appears to be based on a possible lack of protein expression in nature, rather than whether one of ordinary skill in the art would be enabled to make and use the claimed invention. Applicants have provided the SEQ ID NO:2 nucleotide sequence, and one of ordinary skill in the art would be able to express the encoded protein simply by operably linking nucleotide sequence to a promoter as is rather well

known in the art. Accordingly, Applicants assert that they have indeed enabled the making and use of the claimed protein.

In support of the enablement rejection, the Examiner recites general teachings of Alberts et al. with respect to the translational control of ferritin expression and alludes to other examples of in the first full paragraph of page 4 of the Office Action. Applicants respectfully assert that these examples are not of relevance to the enablement of SEQ ID NO:2 in view of the teachings in the specification regarding expression of SEQ ID NO:2 as shown by SEREX expression cloning.

The Examiner also stated that "the working examples do not clearly show that the claimed peptides are in fact actually cancer associated antigens and if they are actually translated into proteins." Office Action, page 4, last sentence of second full paragraph. Applicants again respectfully disagree.

Regarding the assertion that the claimed peptides were not shown to be cancer associated antigens, Applicants note that SEQ ID NO:2 was described as encoding a polypeptide recognized by antibodies only in sera from cancer patients (colon, renal and lung cancer patients, see Table I in Example 4). The protein encoded by SEQ ID NO:2 was not recognized by any normal sera (Table I, Example 4). Accordingly, because the protein encoded by SEQ ID NO:2 is recognized by antibodies from cancer patients and not by antibodies from normal donors (i.e., those without cancer), SEQ ID NO:2 encodes a cancer-associated antigen.

Regarding the assertion that the claimed peptides were not shown to be translated into proteins, Applicants assume that the Examiner meant to say that the nucleic acids were not shown to be translated. This assertion was addressed above; the SEREX cloning procedure requires that the nucleic acids were translated to generate antibodies in cancer patients.

The Examiner also states that "absent evidence that encoded proteins (if encoded) would effectively induce MHC restricted T cell responses, one of [ordinary] skill in the art would not be able to practice the claimed invention without undue experimentation." Office Action, page 4, last sentence of last paragraph. Applicants respectfully disagree.

First, as noted above, Applicants have demonstrated that the proteins are expressed, because without protein expression, no antibodies would have been generated in cancer patients. Second, this same concept provides evidence that MHC restricted T cell responses were effectively induced, in order to provide T cell help for the B cell antibody response.

Third, the law of enablement does not require a description of every aspect of the claimed invention, because it is expected that one of ordinary skill in the art can exercise routine experimentation to make and use the claimed invention. In this regard, Applicants note that it is routine in the art of cancer immunity to derive peptides from the amino acid sequence of a protein known or suspected to be immunogenic. In this case, Applicants have provided evidence of the immunogenicity of the claimed protein by virtue of the protein's isolation using the SEREX method and the demonstration that specific antibodies to the protein encoded by SEQ ID NO:2 are found in cancer patients' sera. Chen et al (*Proc. Nat'l. Acad. Sci. USA* 94:1914-1918, 1997) described the implications of antibody recognition of cancer-associated proteins: "a humoral response implies T cell recognition of the detected antigens by helper T cells. Thus, even though the antigens are initially identified by antibodies, the method reveals tumor products that can then be analyzed in the context of cell-mediated immunity." (page 1914, right column) Such analysis is well known in the art. Accordingly, it would require only routine experimentation for one of ordinary skill in the art to identify peptides useful in the claimed compositions.

Therefore, Applicants respectfully request that the Examiner reconsider and withdrawn the rejections made under 35 U.S.C. 112, first paragraph for lack of enablement.

The Examiner rejected claims 37-40, 63 and 67 under 35 U.S.C. 112, first paragraph, as not enabled by the specification. Applicants respectfully traverse the rejection.

The Examiner cited the Greenberg patent (US 5,470,730) in support of the enablement rejection. Greenberg is reflective of the state of the art in 1990 (its priority date), and is concerned with viral immunotherapy. Greenberg states that clinical trials at that time frequently had used non-MHC restricted cytolytic effector cells, and that there were up to that time some difficulties with the identification of tumor antigens that induce T cell responses. As noted above, the SEREX methodology (which was introduced after the Greenberg patent issued) provides a method in which tumor antigens must have induced a MHC restricted cellular response. Accordingly, the Examiner's citation of Greenberg is believed not to support an enablement rejection.

The Examiner stated that the specification does not provide any description of the proteins that would enable one of ordinary skill in the art to practice the invention. Applicants respectfully disagree. The specification provides the nucleic acid sequence of SEQ ID NO:2,

and provides ample evidence that the protein is expressed. One of ordinary skill in the art knows how to express proteins from nucleic acid molecules given the nucleotide sequence of the nucleic acid molecules. One of ordinary skill in the art also knows how to determine peptides of a protein that are recognized by MHC molecules, by computerized prediction of peptides and/or by empirical experimentation. These are routine activities for those of ordinary skill in the art.

The Examiner stated on page 5 of the Office Action that there was no guidance in the specification for how to induce a T-cell immune response using the claimed peptides, or working examples describing inducement of MHC-restricted T cell responses. Applicants respectfully disagree. First, as noted above, the immune response demonstrated in cancer patients was likely to have involved T cell help. Second, generation of T cell immune responses is well within routine experimentation for one of ordinary skill in the art.

Accordingly, Applicants respectfully request that the Examiner withdraw the enablement rejection of claims 37-40, 63 and 67.

Written Description

The Examiner rejected claim 6 under 35 U.S.C. 112, first paragraph, as not supported by an adequate written description. Applicants respectfully traverse the rejection.

The Examiner stated that the specification does not teach the common structure or features of colon cancer related proteins, and that absent such disclosure, the disclosed sequences are insufficiently descriptive of the claimed genus. Applicants disagree with the Examiner's assertions.

The basic requirement of the written description requirement is that the claimed invention must be described clearly enough to allow one of ordinary skill in the art to recognize that the inventors invented the claimed invention. *Vas-Cath v. Mahurkar* 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991); *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997); *In re Gosteli* 872 F.2d 1008, 10 USPQ 2d 1614 (Fed. Cir. 1989). The requirement is based on the knowledge of the skilled artisan in the particular art: the applicant must convey to one of ordinary skill in the art through the disclosure in the invention that the applicant was in possession of the claimed invention. The *Lilly* case set forth written description requirements relating to nucleic acid sequences; this case does not prohibit definition of a genus of nucleic acid molecules by hybridization to a reference sequence. *Regents of the University of California v. Eli Lilly* 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997). The *Lilly* case merely

states that a DNA molecule must be described by a precise definition, "such as by structure, formula, chemical name or physical properties." *Id.* A genus of nucleic acid molecules encoding a genus of proteins is not routinely defined in the art by a listing of sequences, chemical formulas or chemical names. Instead, the art routinely identifies nucleic acid molecules by hybridization to a particular nucleotide sequence. Hybridization conditions in combination with a reference sequence provide a precise definition of the claimed hybridizing nucleic acid molecules by physical properties. This sort of identification describes the physical properties of a genus of nucleic acid molecules as surely as IR and MS spectra describe the physical properties of a set of chemical compounds.

The claimed invention is a genus of protein molecules that are encoded by SEQ ID NO:2, or by nucleotide sequences that have sufficiently similar structure to permit hybridization to SEQ ID NO:18, or by degenerate molecules, or complements thereof. The alleged lack of a teaching concerning the common features of colon cancer related proteins is not relevant to the claimed invention, which is a much more specific invention. Applicants are not claiming all colon cancer related proteins. Applicants are claiming a set of proteins that are encoded by sequences highly related in structure to SEQ ID NO:2. This disclosed sequence is representative of the genus of nucleic acids that encode the claimed proteins, because all nucleic acid molecules recited in the claims as encoding the claims proteins are highly related in structure (nucleotide sequence) to SEQ ID NO:2 (as the species elected for examination). Thus, SEQ ID NO:2 is in fact a representative species, which, as the Examiner acknowledges on page 6 of the Office Action, can provide an adequate written description.

Applicants have provided one of ordinary skill in the art with a description of representative species and conditions by which other species can be confirmed as belonging to the claimed genus. The Examiner's statement that the specification does not describe species of proteins, even if correct, does not mean that Applicants have not provided one of ordinary skill in the art with sufficient information to appreciate that Applicants were in possession of the claimed invention. This is particularly true in view of the fundamental knowledge of the genetic code possessed by those of ordinary skill in the art, as well as the description of the method used to clone these sequences (SEREX), which requires that the proteins were expressed in order to generate antibodies used in the SEREX procedure.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claim 6 made under 35 U.S.C. 112, first paragraph, for lack of written description.

**Rejections Under 35 U.S.C. 112, Second Paragraph**

The Examiner rejected claims 6 and 38-40 as indefinite in the recitation of complements. The Examiner stated that the size of the complements were unclear. Applicants have amended claim 8 to recite that complements are full length. Applicants do not understand the application of this rejection to claims 38-40, as these claims do not recite complements.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 6 and 38-40 made under 35 U.S.C. 112, second paragraph.

**Rejections Under 35 U.S.C. 101**

The Examiner rejected claims 6, 37-40, 58, 63 and 67 under 35 U.S.C. 101 as lacking patentable utility. Applicants respectfully traverse the rejection.

According to 35 U.S.C. 101, an invention to be patentable must have one or more utilities, which has been interpreted to mean that either a specific and credible utility, or a well established utility must be provided in a patent application. *Manson v Brenner* 383 U.S. 519, 148 USPQ 689 (1966); *Nelson v Bowler* 626 F.2d 853, 206 USPQ 881 (C.C.P.A. 1980). Establishment of one utility is sufficient to meet the statutory utility requirement. *Rey-Bellet v Englehardt* 493 F.2d 1380, 1383, 181 USPQ 453, 454 (C.C.P.A. 1974). As defined in the Training Materials for the Revised Interim Utility Guidelines quoted by the Examiner, a substantial utility is "a practical utility which defines a 'real world' context of use." The PTO Training Materials state that credible with respect to utility means that "the utility is believable to a person of ordinary skill in the art" and that further that the term "refers to the reliability of the assertion of utility based on the logic and facts offered by applicant to support the assertion." As defined in the PTO Training Materials, a well established utility is "a specific, substantial and credible utility which is well known, immediately apparent or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art." A specific utility is one that is "specific to the subject matter claimed," as opposed to general utility applicable to the broad class of the invention.

Applicants have provided one or more utilities that are substantial, credible and specific to the claimed invention. Based on the knowledge of one of ordinary skill in the art, the disclosed utilities are also well-established. The description of the nucleic acid molecules in the specification, coupled with the methodology used to isolate the nucleic acid molecules, makes

immediately apparent to one of ordinary skill in the art at least one specific, substantial and credible utility. For example, the nucleic acid molecules and polypeptides encoded by the nucleic acid molecules can be used in the diagnosis or treatment of conditions characterized by the expression of the tumor associated antigens.

More specifically, the disclosed nucleic acid molecules can be used to generate encoded polypeptides that are useful in such diagnostic and therapeutic methods, particularly in the identification of individuals having specific antibodies that bind to the encoded polypeptides. That the nucleic acid molecules disclosed in the application encode polypeptides recognized by antibodies in the sera of individuals with tumors is known by virtue of the method by which the nucleic acid molecules were isolated (SEREX).

Accordingly, in view of the knowledge of one of ordinary skill in the art with respect to SEREX and antibody recognition, Applicants assert that at least one utility provided in the application is credible, specific and substantial. Applicants based this assertion on the utility definitions provided by the Examiner in the Office Action.

*Credible utility.* The use of nucleic acid molecules to produce proteins is well known and currently available technology. The use of such produced proteins to bind specific antibodies in a variety of immunoassays is well known and currently available. Accordingly, the asserted utility is credible.

The Examiner's asserted that there is no credible utility because the specification teaches that SEQ ID NO:2 was amplified [i.e., expression was measured by PCR amplification] in all tissues tested. In response, Applicants note that the specification teaches that the immune response to the protein encoded by SEQ ID NO:2 (NY-CO-9) was demonstrated in Example 4 to be specific for cancer patients. No antibodies to the protein were found in normal patients' sera. Accordingly, the protein encoded by SEQ ID NO:2 quite clearly has diagnostic value in assaying for specific antibodies in patient sera.

*Specific utility.* The disclosed utility relates to the diagnosis of cancer using the disclosed proteins that are specifically recognized by antibodies produced by individuals bearing tumors. The existence of an immune response against specific proteins of tumor cells is well known. The specificity of the immune response, i.e., antigen-antibody binding, is also well known. The diagnosis of cancer based on antigen-antibody binding is well known. The specific diagnostic utility described in the application is specific for the disclosed nucleic acid molecules and the polypeptides encoded by the nucleic acid molecules. The recognition of the encoded

polypeptides only by antibodies in cancer patient sera is disclosed in the application. The specificity of the diagnostic methods for cancer is disclosed in the application. The utility disclosed is not made by way of "general statements" as asserted by the Examiner.

*Substantial utility*. The disclosed utility is substantial because it is an assay that measures the presence of a material [antibodies] which has a stated correlation to a predisposition to the onset of a particular disease condition [cancer]. Note that the disclosed utility, diagnosis of cancer by determining antigen-antibody recognition, is a "real world" use practiced daily in clinics around the world. Applicants disclosure provides additional proteins that are specifically recognized by the human immune system and thus useful in "real world" diagnostic applications.

Applicants further note that the disclosed utility fits within the definition of "well established" utility. As described above, the utility of using the nucleic acid molecules to produce polypeptides for use in specific assays of immune responses in cancer is specific, substantial, credible, and well known by those of ordinary skill in the art. The utility also would be immediately apparent of one of ordinary skill in the art based on the teachings of the specification and in view of the knowledge of one of ordinary skill in the art.

Applicants thus disagree with the Examiner's statements that "the specification fails to assert any specific and substantial utility for the claimed peptides and proteins," and "the specification fails to disclose a credible utility for the claimed proteins and peptides . . . ." Office Action at page 7.

Moreover, the Examiner's recitation of the Sahin et al. reference does not support a finding of no utility for the claimed protein. The statement of Sahin describes the relative paucity of tumor specific and tumor associated antigens as a backdrop against which the SEREX method is introduced. Applicants also utilized SEREX to identify tumor associated proteins (including SEQ ID NO:2).

Therefore, it is Applicants belief that the Examiner has not met the burden for a *prima facie* showing of lack of utility for the claimed invention, and it is respectfully requested that the rejections of the claims under 35 U.S.C. 101 for lack of utility be withdrawn.

The Examiner also rejected claims 6, 37-40, 58, 63 and 67 under 35 U.S.C. 112, first paragraph because one of ordinary skill in the art would not know how to use the claimed invention in view of the alleged lack of asserted utility. This rejection, which the Examiner bases solely on the aforementioned 35 U.S.C. 101 rejection, should be reversed based on the

clear evidence of utility as described above. Therefore, Applicants respectfully request that the 35 U.S.C. 112 rejection of the claims based on the lack of utility be withdrawn.

In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejections and act favorably upon the claims.

Respectfully submitted,

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Attorney Docket No. L0461/7081
Date: October 15, 2001
**X10/17/01**

**New Section:**

**Related Applications**

This application is a divisional of U.S. Application Serial No. 08/948,705, filed on October 10, 1997, now issued as U.S. Patent 6,043,084.

**Amended Paragraph**

One key methodology is described by Sahin, et al., Proc. Natl. Acad. Sci. USA 92: 11810-11913 (1995), incorporated by reference. Also, see U.S. Patents [Applications Serial No.] 5,698,396 and 6,025,191. All three of these references are incorporated by reference. To summarize, the method involves the expression of cDNA libraries in a prokaryotic host. (The libraries are secured from a tumor sample). The expressed libraries are then immunoscreened with absorbed and diluted sera, in order to detect those antigens which elicit high titer humoral responses. This methodology is known as the SEREX method ("Serological identification of antigens by Recombinant Expression Cloning"). The methodology has been employed to confirm expression of previously identified tumor associated antigens, as well as to detect new ones. See the above referenced patents [applications] and Sahin, et al., supra, as well as Crew, et al., EMBO J. 144: 2333-2340 (1995).

**Amended Claim:**

6.(twice amended) An isolated protein encoded by an isolated nucleic acid molecule selected from the group consisting of:

(a) nucleic acid molecules which encode a cancer associated antigen, and which comprise a nucleotide sequence, the complementary sequence of which hybridizes, under stringent conditions, to at least one second nucleic acid molecule comprising a nucleotide sequence

selected from the group consisting of the nucleotide sequences set forth as SEQ ID NOs: 1, 2, 3, 4, and 5,

(b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and

(c) full length complements of (a) or (b).